

Exhibit 2



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1. Wms.
9/29/00

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the **PATENT APPLICATION** of:

Lo et al.

Application No.: 09/380,696

Our File: SHP-PT048

Filed: November 29, 1999

Date: September 15, 2000

For: NON-INVASIVE PRENATAL DIAGNOSIS

Group: 1655

Examiner: J. Enewold

REPLY PURSUANT TO 37 C.F.R. § 1.111

Commissioner for Patents
Washington, D.C. 20231

Sir:

This Reply is responsive to the Examiner's Action dated April 18, 2000. The Applicants respectfully request that the Application be amended as follows:

IN THE ABSTRACT

Please delete the abstract from the face sheet of the PCT published application and substitute therefor the ABSTRACT submitted herewith on a separate sheet.

IN THE DRAWINGS

A proposed revision to separately identify the individual graphs of Figure 4 as indicated in red on the attached sheet is submitted herewith.

09/25/2000 MPRAASD 00000103 09380696

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IN THE SPECIFICATION

On page 8, line 14, please delete "Figure 4 shows" and insert -- Figures 4a-4l show --.

On page 29, line 2, please delete "fig. 4" and insert -- Figures 4a-4l --.

On page 31, line 14, please delete "fig. 4" and insert -- Figures 4a-4l --.

On page 34, line 19, please delete "Figure 4" and insert -- Figures 4a-4l --.

IN THE CLAIMS

Please amend the following claims:

⁹ ~~N~~. (Amended) The method according to claim ⁸ ~~8~~ wherein the non-Y sequence is a blood group antigen gene [such as the Rhesus D gene].

¹⁰ ~~N~~. (Amended) The method according to claim ⁸ ~~8~~ wherein the non-Y sequence is a gene which confers a disease phenotype in the foetus [, such as the Rhesus D gene].

Please add the following new claims:

²⁶ ~~N~~. The method according to claim ⁹ ~~N~~ wherein the blood group antigen gene is the rhesus D gene.

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27
28. The method according to claim ¹⁰~~N~~, wherein the gene is the rhesus D gene.--

REMARKS

The drawings have been objected to because the views of Figure 4 were not labeled separately. Approval of the proposed drawing changes as indicated on the attached sheet is requested. No new matter has been added.

Applicants have amended the specification to conform with the drawing amendment. An abstract on a separate sheet has been provided as required. No new matter has been added.

Claims 1-26 are pending in the application. A priority claim to GB9704444 (hereinafter "the priority document"), filed March 4, 1997, was objected to with respect to Claims 7-8, 17, 20-21 and 24. Claims 1-26 were rejected under the first paragraph of 35 U.S.C. §112. Claims 10-11 were rejected under the second paragraph of 35 U.S.C. §112. Claims 7 and 17 were rejected under 35 U.S.C. §102(a) as being anticipated by Lo (Lancet, August 1997).

Applicants respectfully traverse the Examiner's priority objection and anticipation rejection of claims 7 and 17 over Lo (Lancet, August 1997). With respect to claims 8, 20-21 and 24, the objection is not ripe since no rejection over intervening art has been made. With

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respect to the Examiner's assertion that claim 7 is not supported by the priority document because it includes no reference to detecting DYS14, Applicants respectfully disagree. Page 8, lines 2-5 of the priority document explicitly refer to amplification of a single copy of Y sequence DYS14.

With respect to claim 17, the Examiner asserts that the priority document does not disclose variations of fetal DNA concentrations over the different stages of gestation. Applicants respectfully disagree. Applicants submit that the priority document clearly describes that variations in the quantity of foetal DNA may occur in some pregnancy-associated conditions such as pre-eclampsia. Specifically, page 2, lines 24-27, specifically refers to differing amounts of foetal DNA being present in the maternal serum or plasma. One skilled in the art would readily understand that this would refer to a variation of foetal DNA concentration at a particular stage of gestation. Further, at the priority filing date, one skilled in the art would have also been aware that foetal DNA generally shows a variation over the course of a pregnancy. In order to monitor whether there is a higher or lower level of foetal DNA compared to normal, it would be desirable to make a comparison with a sample from a similar stage of gestation.

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Although the priority document does not include identical claims as now on file, Applicants respectfully submit that the disclosure of the priority document, as read by one skilled in the art, clearly encompasses rejected claims 7 and 17. Accordingly, the §102 rejection based on Lo (Lancet, August 1997) is traversed as not being prior art to these claims.

The rejection of Claims 1-5 and 9-11 under the first paragraph of 35 U.S.C. §112, as containing subject matter which was not adequately described in the specification, is respectfully traversed. The Examiner contends that there is not adequate description for the detection of the large genus of paternally-inherited non-Y sequences. Although, as noted by the Examiner, there is substantial variability among the species of nucleic acids encompassed in the scope of the claim, Applicants submit that one skilled in the art is aware of a variety of techniques which might be used to detect different nucleic acid species. For example, there are numerous techniques which might be used to detect repeat expansions, single gene mutations, deletions or translocations. These techniques are a matter of routine for one skilled in the art for the analysis of DNA.

Further, the invention does not rely on the identification of any specific paternally-inherited non-Y sequences. The invention resides in the identification of foetal DNA in a serum or plasma sample. One skilled in the art could take advantage of the present

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application describing the presence of foetal DNA in the plasma or serum and apply it to the detection of paternally-inherited non-Y sequences in addition to those which are described. For example, the Examiner has referred to an article by Amicucci et al. which clearly describes detection of an expanded repeat. The Amicucci et al. article clearly demonstrates that the technique as described in the present application may be readily applied to the detection of repeat sequences.

Additionally, Applicants refer the Examiner to a number of other documents which describe analysis of foetal DNA in maternal plasma or serum. Attached herewith are copies of Pertl et al. *Human Genetics* 106(1) - 45-49, 2000 (Abstract), Tang et al. *Clinical Chemistry* 45, 11;1999; 2033-2035, Smid et al. *Clinical Chemistry* 45, 8; 1999; 1570-1572 and Chen et al. *Prenat Diagn* 2000, 20; 355-357. Each of these articles provides an example of the application of the general technique described in the present application to specific sequences. Each of these articles refers to the work done by the inventors of the present application disclosed in Lo et al. In particular, these articles refer to Lo et al. where it describes detection of foetal DNA in maternal plasma and serum and describes the technique to a variety of different sequences. Moreover, the articles cited above demonstrate that microsatellite alleles which differ by a very small number of nucleotides between the mother and baby, that is by 2 base pairs, are detectable using the technology described in the present

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application. Microsatellites are essentially polymorphic pieces of DNA, which are different between different individuals by virtue of insertions or deletions of a small number of base pairs. The paper by Chen et al. describes the successful diagnosis of a paternally-inherited reciprocal translocation.

Additionally, there are numerous types of mutations that might be detected, in accordance with the present invention. The Examiner has discussed whether the technique is applicable for detecting small differences between the mother and foetus and has highlighted three categories, namely, single gene mutations, deletions, and translocations. The attached articles clearly demonstrate that a wide variety of different polymorphisms may be detected in accordance with present application. Applicants submit that there is sufficient description in that the key features of the claimed technique have been described in the Application, and, in particular, one skilled in the art is instructed to use maternal plasma or serum for the detection of foetal DNA. Although there are a wide variety of different types of polymorphisms which could be detected in connection with the present application, such polymorphisms and techniques for analysis of DNA are simply a matter of routine for one skilled in the art. Therefore, it is not necessary for the Applicants to set out each of the many ways in which DNA might be analyzed. The description is sufficient simply by instructing one skilled in the art to carry out a suitable analysis. The additional documents, attached

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hereto, clearly demonstrate that one skilled in the art is readily able to apply the teachings of the present application to any one of the well known techniques for detection of DNA with a view to analysis of foetal DNA in paternal plasma or serum.

Applicants respectfully traverse the rejection of Claims 1-26 under the first paragraph 35 U.S.C. §112, on the basis of lack of enablement for a general detection method performed on serum or plasma for detecting fetal nucleic acid at any time during pregnancy or associated with disease phenotype and serum. The Examiner refers to Lo et al. (*New England J. of Med.*, Vol. 339, No. 24, pages 1734-8) and suggests that the claims are only enabled with respect to detecting the presence of paternally-inherited foetal DNA in maternal plasma after 15 weeks of gestation. The Examiner has indicated that there is unpredictability in detecting foetal DNA in plasma before the fifteenth week of gestation. However, Applicants respectfully submit that the specification is enabled across the scope of the breadth of the claim for a detection method performed on serum or plasma of pregnant women to detect any foetal DNA during the course of pregnancy. Although the article cited by Examiner suggests that reliable results for foetal RHD status can be determined from the fifteenth week of gestation, the paper nevertheless demonstrates that testing prior to 15 weeks of gestation is already useful.

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The Examiner has cited some of the Applicants' own comments in the article of Lo et al., *Annals of Medicine*, Volume 31, 5: 1999; 308-312. As with all technologies, it can be expected that improvements in the technology may arise. For example, it is likely that improvements will be made to enhance sensitivity of the techniques. However, this is not to say that the techniques can not be used as a diagnostic method across the scope of the claims. Clearly, the statements quoted by the Examiner in the *Annals of Medicine* cannot be seen as a suggestion that the technique does not in itself work effectively.

With respect to the dividing line of 15 weeks, the article by Lo et al. referred to by the Examiner merely states that for RHD, PCR tests are reliable beginning in the second trimester. This is not to say that such tests can not be useful when carried out before the second trimester. For example, if a potential problem were highlighted in a test carried out before the second trimester, this problem could be used as part of a diagnosis such as to identify women who require close monitoring in later stages, for example to confirm a provisional diagnosis. Thus, it may be possible to identify such things as a foetus at risk of foetal hemolytic disease before 15 weeks of pregnancy and highlight that pregnancy for enhanced surveillance.

There are also numerous papers showing that the technology can be used prior to the 15th week of gestation. In Lo et al., *American Journal of Human Genetics* of 1998, 62; 768-

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775, the authors show that foetal DNA can be detected from maternal serum at the seventh week of gestation. Amicucci et al. demonstrates that the technology can be used at the tenth week of gestation. Smid et al., *Clinical Chemistry* 1999, 45;1570-1572 demonstrates that the method is applicable between the seventh and fourteenth weeks of gestation.

Additionally, the Examiner also refers to a number of papers as suggesting that there are potential problems with the technique and that to a certain extent the claims are based on hypothesis. As highlighted above, the present invention results in the new identification that foetal DNA is present in maternal plasma or serum. Many of the points highlighted by the Examiner would be considered to be a matter of routine experimentation to one skilled in the art of DNA detection, to identify the most appropriate technique for a particular required diagnosis. The person skilled in the art has a broad range of techniques available for the detection of DNA in a sample. Thus, one skilled in the art, equipped with the teaching of the present patent application, would be readily able to overcome any such potential problems mentioned by the Examiner. Indeed, there is much literature, such as the articles referred to above, which demonstrates that the technique has been successfully applied to other sequences.

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The Examiner further suggests that there may be a problem in connection with using material serum and that increased amount of maternal DNA can be found. The Examiner quotes Lo et al.:

The results indicated that a higher maternal background is present when serum is used which may be detrimental for the detection of foetal DNA, especially when less sensitive detection methods are used.

Applicants submit that one skilled in the art would understand simply that a higher maternal background may be present where serum is used, and that it may be preferable to use a more sensitive detection method. However, as highlighted above, this statement does not in any way suggest that the technique can not be used. The statement merely suggests that the technique should be optimized given the particular circumstances. This is simply a straightforward matter of application of an appropriate DNA detection method.

The Examiner has highlighted some problems in using serum samples, highlighted by Bischoff et al. However, one skilled in the art would simply take appropriate action to avoid the specific problems highlighted in this article. The article does not suggest that the method would in any way not work simply because serum DNA was being used. In any event, there are a number of papers which have used maternal serum reliability for detection of foetal DNA, namely, Lo et al. *American Journal of Human Genetics* Supra, Lo et al., *Clinical Chemistry* 1999, 45;184-188 (abstract attached).

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In summary, the, various documents cited by the Examiner do not suggest that the present technique would not be successful. Improvement of the process or selection of the most appropriate of DNA analysis is simply a matter of routine experimentation which would be carried out by one skilled in the art based on the readily available techniques of DNA detection.

With respect to the rejection of Claims 10 and 11 under 35 U.S.C. §112, Applicants have amended these claims to delete the phrase "such as" objected to by the Examiner. New dependent claims 27 and 28 have been added. Applicants believe these claims are now in condition for allowance.


It is respectfully submitted that the pending claims as amended are now in condition for allowance. Reconsideration, approval of the drawing amendment, and allowance are respectfully requested.



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Respectfully submitted,

Lo et al.

By 
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Suite 400, One Penn Center
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Philadelphia, PA 19103


CFK/JMO/dag

Attachments: Pertl et al. *Human Genetics*
Tang et al. *Clinical Chemistry*
Smid et al. *Clinical Chemistry*
Chen et al. *Prenat Diagn*
Lo et al., *American Journal of Human Genetics*
Lo et al., *Clinical Chemistry*

Enclosures (2)



ABSTRACT

 The invention relates to a detection method performed on a maternal serum or plasma sample from a pregnant female, which method comprises detecting the presence of a nucleic acid of foetal origin in the sample. The invention enables non-invasive prenatal diagnosis including for example sex determination, blood typing and other genotyping, and detection of pre-eclampsia in the mother.

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ECT/GB99/00698

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~~Fig. 4~~

11

CASE S-1

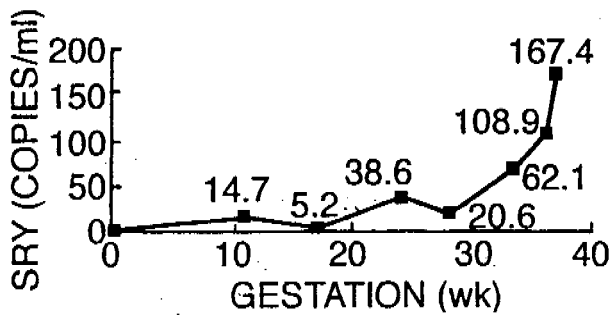


Fig. 4a

CASE S-3

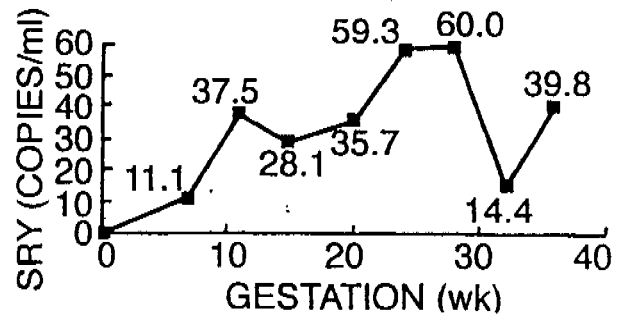


Fig. 4b

CASE S-4

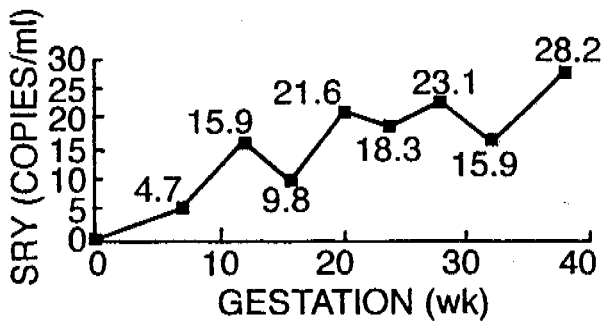


Fig. 4c

CASE S-5

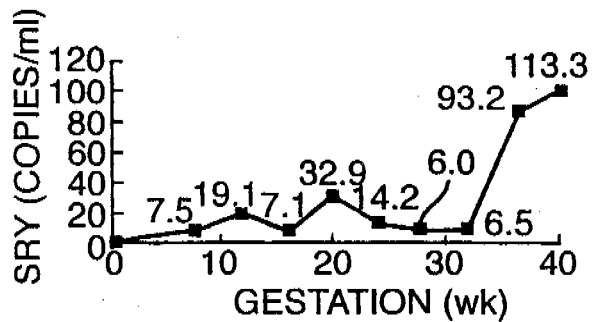


Fig. 4d

CASE S-6

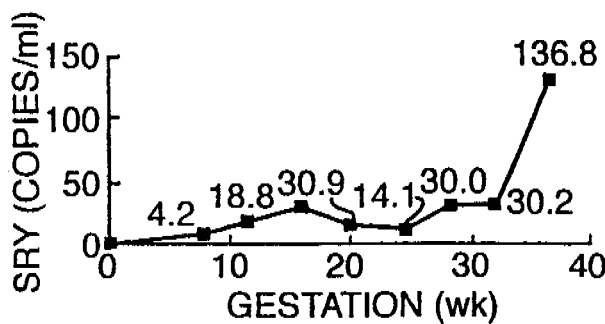


Fig. 4e

CASE S-7

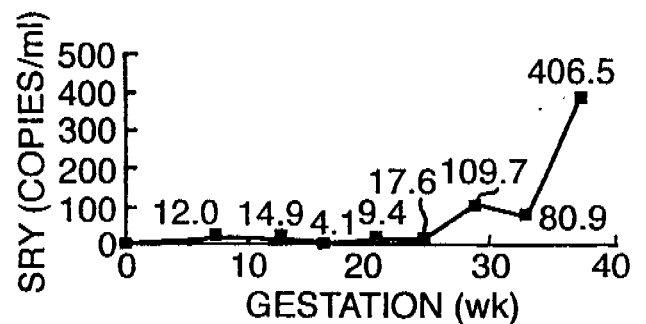
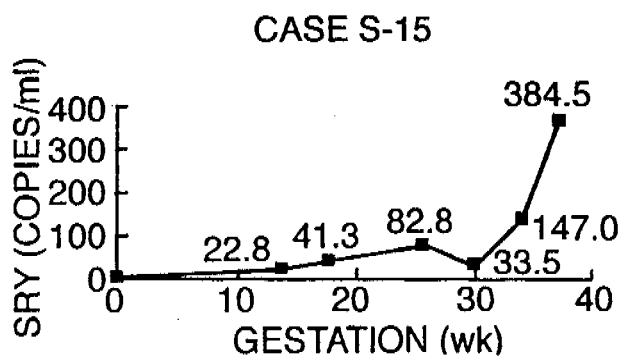
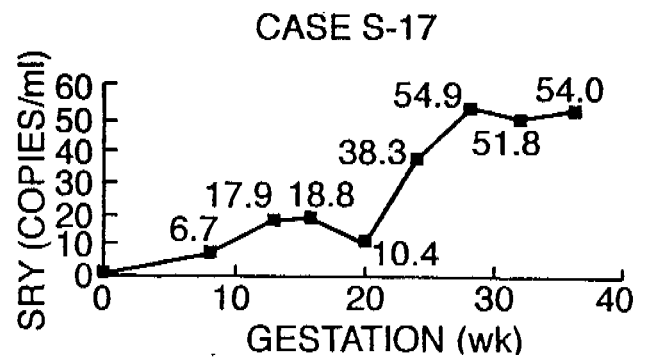
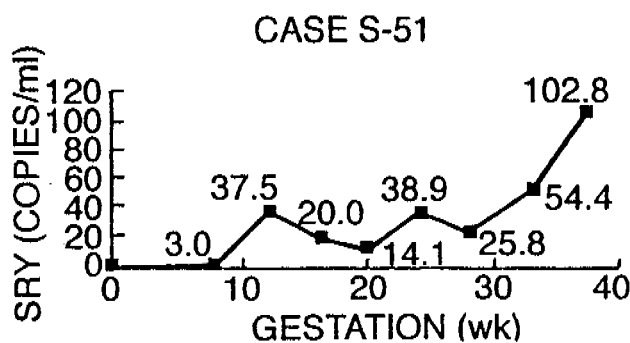
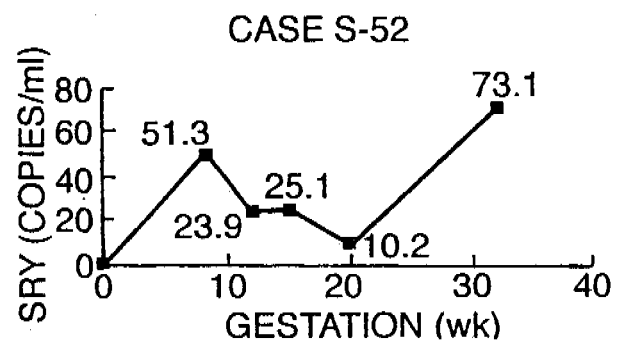
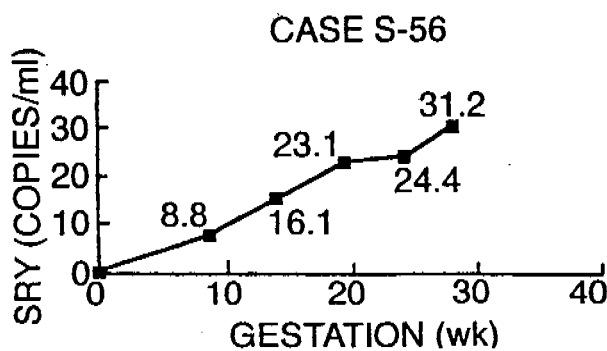
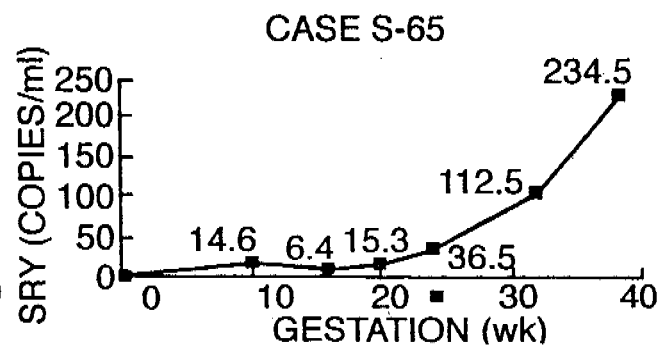
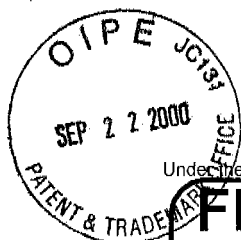


Fig. 4f

~~WO 98/39474~~~~PCT/GB98/00690~~

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~~Fig. 4(Cont.)~~*Fig. 4g**Fig. 4h**Fig. 4i**Fig. 4j**Fig. 4k**Fig. 4l*



Volpe and Koenig, P.C. Revision of PTO/SB/17 (12/99)
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 See 37 C.F.R. §§ 1.27 and 1.28.

TOTAL AMOUNT OF PAYMENT (\$)**\$208.00**

Complete if Known

Application Number	09/380,696
Filing Date	November 29, 1999
First Named Inventor	Lo et al.
Examiner Name	Enewold, J.
Group / Art Unit	1655
Attorney Docket No.	SHP-PT048

METHOD OF PAYMENT (check one)

1. ☐ The Commissioner is hereby authorized to charge the fees indicated hereon:

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Code (\$)	Small Entity Code (\$)	Fee Description	Fee Paid
101 690	201 345	Utility filing fee	
106 310	206 155	Design filing fee	
107 480	207 240	Plant filing fee	
108 690	208 345	Reissue filing fee	
114 150	214 75	Provisional filing fee	

SUBTOTAL (1) (\$)

2. EXTRA CLAIM FEES

Total Claims	Extra Claims	Fee from below	Fee Paid
28	2	\$9.00	\$18.00
Independent Claims	3	\$39.00	0
Multiple Dependent			

**or number previously paid, if greater; For Reissues, see below

Large Entity Code (\$)	Small Entity Code (\$)	Fee Description	Fee Paid
103 18	203 9	Claims in excess of 20	
102 78	202 39	Independent claims in excess of 3	
104 260	204 130	Multiple dependent claim, if not paid	
109 78	209 39	** Reissue independent claims over original patent	
110 18	210 9	** Reissue claims in excess of 20 and over original patent	

SUBTOTAL (2) (\$)**18.00**

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Code (\$)	Small Entity Code (\$)	Fee Description	Fee Paid
105 130	205 65	Surcharge - late filing fee or oath	
127 50	227 25	Surcharge - late provisional filing fee or cover sheet.	
139 130	139 130	Non-English specification	
147 2,520	147 2,520	For filing a request for reexamination	
112 920*	112 920*	Requesting publication of SIR prior to Examiner action	
113 1,840*	113 1,840*	Requesting publication of SIR after Examiner action	
115 110	215 55	Extension for reply within first month	
116 380	216 190	Extension for reply within second month	\$190
117 870	217 435	Extension for reply within third month	
118 1,360	218 680	Extension for reply within fourth month	
128 1,850	228 925	Extension for reply within fifth month	
119 300	219 150	Notice of Appeal	
120 300	220 150	Filing a brief in support of an appeal	
121 260	221 130	Request for oral hearing	
138 1,510	138 1,510	Petition to institute a public use proceeding	
140 110	240 55	Petition to revive - unavoidable	
141 1,210	241 605	Petition to revive - unintentional	
142 1,210	242 605	Utility issue fee (or reissue)	
143 430	243 215	Design issue fee	
144 580	244 290	Plant issue fee	
122 130	122 130	Petitions to the Commissioner	
123 50	123 50	Petitions related to provisional applications	
126 240	126 240	Submission of Information Disclosure Stmt	
581 40	581 40	Recording each patent assignment per property (times number of properties)	
146 690	246 345	Filing a submission after final rejection (37 CFR § 1.129(a))	
149 690	249 345	For each additional invention to be examined (37 CFR § 1.129(b))	
Other fee (specify) _____			
Other fee (specify) _____			

* Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$)**190**

SUBMITTED BY

Name (Print/Type)	C. Frederick Koenig III, Esquire	Registration No. (Attorney/Agent)	29,662	Telephone	215-568-6400
Signature		Date	9/15/00		

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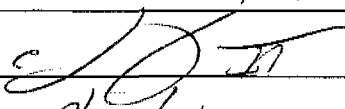
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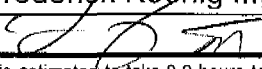
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TRANSMITTAL FORM <i>(to be used for all correspondence after initial filing)</i>	Application Number	09/380,696	
	Filing Date	November 29, 1999	
	First Named Inventor	Lo et al.	
	Group Art Unit	1655	
	Examiner Name	Enewold, J.	
Total Number of Pages in This Submission	20	Attorney Docket Number	SHP-PT048

ENCLOSURES (check all that apply)		
<input checked="" type="checkbox"/> Fee Transmittal Form <input checked="" type="checkbox"/> Fee Attached <input checked="" type="checkbox"/> Amendment / Response <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input checked="" type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Response to Missing Parts/Incomplete Application <input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Assignment Papers (for an Application) <input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition Routing Slip (PTO/SB/69) and Accompanying Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Small Entity Statement <input type="checkbox"/> Request for Refund	<input type="checkbox"/> After Allowance Communication to Group <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input type="checkbox"/> Appeal Communication to Group (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input checked="" type="checkbox"/> Additional Enclosure(s) (please identify below): Attachments (6 Articles); Marked Up Drawing sheets (2 pgs.); Abstract (1 pg.)
Remarks		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT		
Firm or Individual name	C. Frederick Koenig III, Esquire VOLPE and KOENIG, P.C.	Reg. No. 29,662
Signature		
Date	9/15/00	

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